REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining in this application be allowed.

Amendments

The specification was amended at page 5 and in the paragraph bridging pages 9 and 10 to correct several typographical/inadvertent errors.

Claims 1-10 were canceled and replaced with new Claims 12-18. In addition, Claim 11 was canceled without prejudice or disclaimer. Applicants reserve the right to file a continuation application directed to the subject matter of previously presented Claim 11.

Newly presented Claim 12 corresponds to previously presented Claim 1 with the exceptions:

this claim is now directed to a method for the treatment of chronic fatigue syndrome in a mammalian patient which disease is characterized by an excessive level of IL-6 cytokines in the patient (see, for example, page 2, lines 14-28, of the specification);

this claim recites selecting a patient suffering from or at risk of suffering from chronic fatigue syndrome (see, for example, page 2, lines 23-28, of the specification);

this claim recites withdrawing an aliquot of blood comprising blood cells from said patient (see, for example, page 4, lines 9-10, of the specification) ;

this claim recites subjecting these cells to stress comprising both oxidative and ultraviolet conditions simultaneously (see, for example, previously presented Claim 4);

this claim recites administering to the patient an effective amount of stressed blood cells such that upon administration the level of IL-6 in the patient is reduced (see, for example, page 9, lines 20-23).

Newly presented Claims 13-18 correspond to previously presented Claims 5-10.

Applicants submit that no new matter has been introduced by these amendments. Entry of these amendments is earnestly solicited.

Restriction Requirement

The restriction requirement set forth in the Office Action of October 21, 2003 (paper no. 7) was repeated and made final. However, upon entering the finality of this restriction requirement, previously restricted Claim 11 was recombined into elected Group III. In view of the finality of the restriction requirement, newly presented Claims 12-18 correspond to use of stressors comprising both oxidative conditions and ultraviolet conditions simultaneously. Applicants reserve the right to file a divisional application directed to the subject matter of non-elected Groups I and II as defined in the October 21, 2003 Office Action.

Claim to Foreign Priority

Paragraph 2 of the Office Action acknowledges Applicants' claim to foreign priority but confirms that certified copies of the priority applications have not been filed pursuant to the provisions of 35 U.S.C. §119. Accordingly, submitted concurrently herewith are certified copies of Canadian Patent Application Serial Nos. 2,327,631 and 2,327,628 submitted in accordance with 35 U.S.C. §119.

Brief Description of the Drawings

The Office Action objects to the specification because it allegedly fails to contain a Brief Description of the Drawings. Reference is made to page 3, lines 13-15, of the specification which contains this description. Withdrawal of this objection is requested.

Rejection Under 35 U.S.C. §112, first paragraph

Claims 1-11 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly non-enabling for treatment or prophylaxis of any inflammatory disease, including chronic fatigue syndrome, by use of the methods of this invention and require undue

experimentation. For the following reasons, Applicants submit that this rejection has been obviated by the now presented claims.

Initially, Applicants note that the Office Action acknowledges that the application is enabling for a process of decreasing expression of IL-6 cytokines from cells in mammalian patients.

Secondly, Applicants maintain that this rejection has been obviated by virtue of the fact that newly presented Claim 12 does not recite an inflammatory disease but rather recites treatment and prophylaxis of chronic fatigue syndrome (CFS) in a mammalian patient characterized by an excessive level of IL-6 cytokines in the patient. The specification at page 2, lines 23-28, clearly recites that the role of excessive amounts of IL-6 in CFS in a mammalian patient. Further, the bridging paragraph at pages 9 and 10 of the specification recites that down regulating IL-6 correlates to methods for treatment or prophylaxis of CFS.

Nowhere does newly presented Claim 12 recite an inflammatory condition but rather correlates treatment or prophylaxis of CFS to down regulation of IL-6 – a method for which the Office Action already acknowledges as enabling.

Accordingly, Applicants maintain that, as presented, Claim 12 is clearly enabled and is acknowledged as such by the Office Action.

Applicants traverse this rejection to the extent that the USPTO applies such against newly presented Claims 12-18. Specifically, to establish a *prima facie* case of lack of enablement, the burden is on the USPTO to provide objective evidence to dispute the enablement provided by the specification and to explain why it doubts the truth or accuracy of the disclosure. *In re Marzocchi,* 439 F.2d 220, 224 (CCPA 1971); *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993).

In this case, the USPTO has either overlooked or ignored the explicit teachings in the specification which provide greater guidance than the language of the instant rejection would suggest. The specification teaches and the Office Action acknowledges that the

methods of this invention decreases the expression and/or the activity of IL-6.[1] The specification further teaches and provides literature references supporting the correlation of IL-6 to CFS.[2] The Office Action fails to explain why these teachings and references would not provide the skilled artisan with the requisite correlation of IL-6 to CFS. At best, the Office Action cites Feldman, et al. as stating that:

"While it is not difficult to study the pathogenesis of animal models of disease, there are multiple constraints on analyses of the pathogenesis of human disease..."

Reliance on Feldman as it relates to rheumatoid arthritis is misplaced since Applicants' now presented claims are not directed to this disease.

Moreover, the Office Action has failed to explain why rheumatoid arthritis is germane to chronic fatigue syndrome. In this regard, the articles cited in the specification provide the requisite correlation to the level that one skilled in the art would reasonably correlate reduction in IL-6 levels with treatment of CFS and nothing in Feldman teaches otherwise. In this regard, it is well established that clinical studies or animal data are not necessary to enable the application provided that the data presented provides a reasonable correlation between the data presented and the claimed methods.

As to reliance on Cochlovius, et al., Applicants note that the claimed invention uses the patient's own blood and, accordingly, reference to xenograft transplantation is not relevant to the now claimed invention. Reliance on Van Noort, et al. is also misplaced. Table III of Van Noort is directed to models of several autoimmune diseases none of which include CFS.[3] Cited page 176 of Van Noort is not directly related to treatment of autoimmune diseases but, rather, states that:

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[1] See, for example, page 3, section 5, first paragraph of the Office Action as well as the paragraph bridging pages 9 and 10 of the specification. See also the Example of this application including FIG. 2.

[2] See, for example, page 2, lines 23-28, of the specification as well as the paragraph bridging pages 9 and 10 of the specification.

[3] The Office Action referenced Table III at page 178 of Van Noort, et al. However, this table is at page 168. If the Office Action intended reference to another section of Van Noort, et al. Applicants respectfully request clarification.

"As in other autoimmune diseases, however, genetic, environmental and hormonal factors clearly affect disease."

When read in context with the proceeding sentence, the relevant quotation should have been:

"However, a multitude of different viruses and bacteria have been implicated in the development as has been the role of stress proteins, most notably hsp60. As in other autoimmune diseases, however, genetic, environmental and hormonal factors clearly affect disease."

Clearly, this cited section is reciting the pathogenesis of autoimmune diseases such as rheumatoid arthritis (RA) and is not relevant to the treatment of these diseases. Moreover, nothing in this cited section relates to or otherwise contradicts the teachings of the application and the references cited therein showing a correlation between IL-6 and CFS. Absent such teachings, the disclosure of Van Noort, et al. is misplaced.

Still further, the specification provides detailed teachings as to both a dosing level and schedule for dosing for treating patients with an IL-6 mediated disorder which, as above, includes CFS.[4]

In view of the above, Applicants maintain that the currently presented claims are clearly enabled. Withdrawal of this rejection is requested.

Rejections Under 35 U.S.C. §102

Claims 1, 2, 4-6, 8 10 and 11 stand rejected under 35 U.S.C. §102(a) over WO 00/06703 as evidenced by Kuby.

Claims 1, 2, 4-6, 8 10 and 11 stand rejected under 35 U.S.C. §102(b) over WO 98/07463 or by U.S. Patent No. 5,980,954.

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[4] See, for example, the section of the specification starting at page 8, line 24, and continuing to page 10, line 3.

Applicants submit that both of these rejections are now moot in view of the fact that the recitations of previously presented Claim 3 (not included in these rejections) has been incorporated into the now presented claims.

Withdrawal of these rejections is earnestly solicited.

Rejections Under 35 U.S.C. §103(a)

Claim 3 stands rejected under 35 U.S.C. §103(a) over Bolton, International Patent Application Publication No. WO 98/07436 ('436 application) or Bolton, U.S. Patent No. 5,980,954 ('954 patent) or Spaner, International Patent Application Publication No. WO 00/06703 ('703 application) each in view of CDC Report (1999).[5] For the following reasons, this rejection is traversed.

Initially, the test for non-obviousness articulated by the Court of Appeals for the Federal Circuit in *In re Vaeck* requires consideration of at least the following factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should practice the claimed invention; and (2) whether the prior art would also have provided a reasonable expectation of success to such a skilled artisan. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The first requirement goes to the question of motivation, and refers to a line of well established cases that there must be some logical reason at the time of the invention for modifying the cited references along the lines of the invention; otherwise the use of the teachings as evidence of non-obviousness will entail prohibited hindsight. *Ex parte Stauber and Eberle*, 208 USPQ 945 (Bd. App., 1980).

Secondly, Applicants maintain that a *prima facie* case of obviousness has not been established because there is no suggestion or motivation, outside Applicants' own disclosure, to modify the cited art in a manner necessary to arrive at the claimed invention. Nor is there any reasonable basis in the art to reasonably expect that the prior

[5] The '463 application is related to the '954 patent since they both claim priority to a common US application, U.S. Serial No. 08/754,348.

art, so modified, would provide for efficacious results demonstrated by the claimed invention.

Specifically, the now claimed invention recites a method for the treatment or prophylaxis of chronic fatigue syndrome in a mammalian patient which is characterized by an excessive level of IL-6 cytokines in said patient. The method comprises first selecting a patient suffering from or at risk of suffering from chronic fatigue syndrome (CFS). Next an aliquot of blood comprising blood cells is withdrawn from the patient and then the blood cells are subjected extracorporeally to stress comprising both oxidative conditions and ultraviolet conditions simultaneously. An effective amount of the so stressed mammalian blood cells is administered to the patient whereupon the level of IL-6 cytokines in the patient is reduced.

Central to the claimed invention is the treatment or prophylaxis of CFS in a mammalian patient with stressed blood cells which results in a reduction of IL-6 cytokine levels in the patient.

Contrarily, and as acknowledged by the USPTO, neither of the '436 and the '703 applications nor the '954 patent are directed to treating CFS. Moreover, none of these references recite reduction of IL-6 levels in a mammalian patient by the use of stressed blood cells as per the methods claimed herein.

Specifically, rather than addressing IL-6 levels in the treated patient, these references are concerned with the characteristics of treated blood as compared to untreated blood. For example, the '954 patent states that the treated blood has at least one of the following characteristics:

a) increased numbers of lymphocytes and other leucocytes, exhibiting a condensed apoptotic-like morphology;

b) a release of specific proteins from the cell surface of the blood leucocytes, including the MHC Class II molecule HLA-DR, resulting in a reduction in the number of cells expressing such surface proteins;

c) an upregulation in the expression of certain cell surface markers for example CD-11b, a component of the ligand for the cell adhesion molecule ICAM-1;

certain T-cell regulatory molecules;

d) an increase in the amount of heat shock protein HSP-60 in the plasma; and

e) a decrease in HSP-72 within the lymphocytes.

Similar characteristics for the treated blood compared to the untreated blood are found in the '436 application in the paragraph bridging pages 6 and 7 thereof.

Such characteristics are recited as possibly resulting in preferential interactions of the treated cells to antigen presenting cells thereby resulting in preferential phagocytosis.[6] Moreover, the '954 patent recites that the autovaccine of that invention upregulates the TH2 cells thereby increasing the secretion of regulatory cytokines.[7] Nowhere does it mention down regulation of TH1 cells, in general, or IL-6 cytokines, in particular.

Clearly, one skilled in the art would not be motivated by the teachings of either of these references, standing alone or in combination with each other, to arrive at the now claimed invention.

As to the '703 application, this reference recites cellular compositions useful in the alleviation of complications following allogeneic bone marrow transplantation such as those arising in graft versus host disease. The cellular composition of the '703 application comprises T-cells obtained from an allogeneic donor which T-cells have been subjected to *in vitro* oxidative stress so as to down-regulate the destructive allogeneic response such T-cells induce upon administration to the patient. In one embodiment, the stressed T-cells exhibit an altered cytokine population evidenced by a reduction in interferon-γ and tissue necrosis factor-α.[8]

Clearly, one skilled in the art would not be motivated by the teachings of this reference, standing alone, to arrive at the now claimed invention. Specifically, this

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[6] See, for example, the paragraph bridging pages 7 and 8 of the '436 application. Also see, for example, Col. 4, lines 36-64, of the '954 patent.

[7] See, for example, Col. 5, lines 43-52, of the '954 patent.

[8] See, for example, page 5, lines 26-28, of this application.

reference is directed solely to minimizing a destructive allogeneic response as part of the etiology of graft versus host disease. The Office Action fails to recite why the skilled artisan would correlate such treatment to CFS let alone to the treatment of CFS by reducing the level of IL-6 cytokines.

Reference to the cited secondary reference fails to cure the deficiencies of the primary references noted above. Specifically, it is well established law that the mere fact that references can be combined to arrive at the claimed invention does not render a *prima facie* case of obviousness unless there is some motivation to combine the references coupled with a reasonable expectation of success. *In re Vaeck, supra.*

The secondary reference, a CDC article on CFS, was relied upon in the Office Action to establish that CFS is an inflammatory disease mediated by excess inflammatory cytokine production. However, such a statement is an over characterization of this reference. For example, a possible cause for CFS recited at page 10 of the CDC report, states that a viral infection induces excessive production of inflammatory cytokines and that through a cascade of immunological events leads to a continuous production of peroxynitrite levels *in vivo*. The CDC article then recites that this continuous production of peroxynitrite leads to CFS and, accordingly, this cycle must be stopped in order to treat CFS. This article concludes that this cycle can be stopped by 1) treating the underlying viral infection with antiviral agents and those that shift the Th1:Th2 ratio, 2) treating the inflammation, and 3) supporting the nitric oxide system.

Notwithstanding the above, there is no disclosure in the CDC article of suppressing the IL-6 levels in the prophylaxis or treatment of CFS nor is there any basis to conclude from this article that a skilled artisan would reasonably expect that such a suppression would be successful. In fact, the CDC article require a tripartite approach to treating CFS.

Absent such disclosure, the combination of the CDC article with the primary references (in any combination) forms an improper basis for maintaining a rejection under 35 U.S.C. §103(a). *In re Vaeck, supra.*

Withdrawal of this rejection is requested.

Claims 7 and 9 stand rejected U.S.C. §103(a) over the '436 application, the '954 patent or the '703 application. For the following reasons, this rejection is traversed.

Initially, Applicants note that Claims 7 and 9 have been canceled and have been replaced by new Claims 15 and 17. In order to expedite prosecution, this rejection is applied against new Claims 15 and 17.

Secondly, as to this rejection, both of these claims depend directly or indirectly from Claim 12 which Applicants maintain is patentably distinct over the cited references. Accordingly, to the extent that the independent claim is free of this rejection, claims dependent therefrom are likewise free of this rejection.

Withdrawal of this rejection is earnestly solicited.

[**X**]The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date 6-28-04 By _____

FOLEY & LARDNER LLP
Customer Number: 38706
Telephone: (650) 856-3703
Facsimile: (650) 856-3710

Gerald F. Swiss
Attorney for Applicant
Registration No. 30,113